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IMPACT OF PESTICIDE (FENITROTHION) ON AQUATIC AND TERRESTRIAL ANIMALS: A REVIEW

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Pesticide contamination has become a significant public health problem globally because of their widespread use in the agriculture sector to increase crop yield and quality. The organophosphorus pesticides (OPs) are extensively used for insect handling in agriculture due to their effectiveness against the insects and the restricted staying power in the environment. OPs can prevail prolong in the natural environment, causes pollution issues and produce a major problem to humans, animals and nature. The extensive application of OPs in public health and agricultural programs causes critical environmental pollution, which accounts for serious health issues due to acute or chronic poisoning in the living creatures. The Fenitrothion (FNT), from the organophosphate family, is the contact insecticide and the selective acaricide. This review article focuses on the adverse effects of pesticides on targeted and non-targeted organisms, including terrestrial and aquatic life. It includes organophosphates and their toxicity on humans and animals. The main focus is on Fenitrothion, its mechanism and its adverse toxic effect on animals and humans. Adverse effects of Fenitrothion (FNT) on blood cells, immunity, kidney, liver, reproductive system, genetic material, and other aspects are also studied. Oxidative stress has also been included as it is the main factor in pesticides. The objective of this review article is to precisely cover pesticides, mainly FNT.
Keywords: Pollution, public health pests, agriculture, pesticides, organochlorine, Fenitrothion, systemic toxicity.

INTRODUCTION

Agriculture is a significant division to provide food for all humans and animals on the planet. This is remarkable, i.e., the total population is estimated to rise 7–8 billion till 2030, to almost 10 billion people till 2050 (Serraj *et al.,* 2019; Firth *et al.,* 2020; Talaviya *et al.,* 2020). Agriculture presently occupies almost 40% of the total surface area (Williams *et al.,* 2020). The agriculture division needs to raise its production by up to three times its current level due to the continual expansion in the world population. Pesticides are used in large quantities to control illnesses, weeds, insect infestations, and other issues in the agriculture division to increase productivity (Chen *et al.,* 2020). The reproductive systems of people and wildlife are also harmed by environmental contaminants. These toxicants are responsible for endocrine disruption and changes in testicular function (Manfo *et al.,* 2014). Because these pollutants can mimic natural oestrogens and alter steroidogenesis, spermatogenesis, and the functioning of the Leydig and Sertoli cells, male fertility (sperm count and quality) has recently reduced as a result of exposure to environmental contaminants (Mathur *et al.,* 2011). Pesticides are chemical compounds used to control a wide range of pests and disease carriers, such as arachnids, rats, mosquitoes, and mice. Organophosphates have replaced organochlorine pesticides as the most widely used pesticides worldwide due to their low persistence, good degradability, lesser toxicity, and lower persistence in mammalian systems compared to organochlorines (Seiber *et al.,* 2011; Qiu *et al.,*2016). Organophosphorus pesticides (Ops) are prevalent because of their low cost and superior pest control capabilities (Li *et al.,* 2014). The widespread use of these pesticides also pollutes the soil, water, and air. Pesticides can infect animals and plants in areas where they have not been treated because of their vast range of dissemination in the air (Letcher *et al.,* 2010). This type of contamination can also arise from other processes, e.g., water eutrophication, groundwater contaminations (Zhang *et al.,* 2015) and greater incidence of soil bacteria (Itoh *et al.,* 2014). The residue of OPs can persist in the natural environment for an extended period, creating

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contamination and posing a risk to humans, animals, and the ecosystem (Ciucu *et al.,* 2003; Geremedhin *et al.,* 2013). FNT, an organophosphorus pesticide sprayed on cotton, fruit orchards, rice, cereals, and vegetables, kills rice stem borers, flour beetles, wheat bugs, coffee leaf miners, locusts, grain weevils, and beetles. It is frequently used in the home to manage cockroaches, flies, mosquitoes, and termites (Calatayud *et al.,* 2018; Willner *et al.,* 2018; Patel *et al.,* 2019). Tolerable daily consumption of FNT by food is 0=0.005 mg/kg, according to the World Health Organization (WHO). Several organophosphorus insecticides, such as parathion and methyl parathion, were prohibited in several states, including Japan. Despite this, FNT is still widely used in agriculture, even in nations where it is prohibited. FNT accumulation in the environment is inescapable (Sánchez *et al.,* 2008; Pundir *et al.,* 2019; Chen *et al.,* 2020), leading to bio-magnification via food chain entry, posing a significant threat to entire ecosystems.

Because organophosphorus insecticides are potentially harmful to other creatures, they should be handled with caution and disposed of properly (Govindasamy *et al.,* 2018). Because of their widespread use, organophosphorus insecticides will inevitably find their way into surface and groundwater supplies, posing severe health and environmental risks (Bolat *et al.,* 2018).

Pesticides are a significant source of pesticides in aquatic environments for a variety of reasons, including disease vector control (e.g., malaria), management of residential as well as commercial, management of grass field green spaces and water reserves (e.g., ponds), treatment of livestock and domesticated animals, resin, fresh fruits and vegetables, paints, and apartments (e.g., insect repellents), and preservation of aquatic environments (Gilbert *et al.,* 2009; Szpyrka *et al.,* 2015; Rousis *et al.,* 2017; Hegazy *et al.,* 2020). Additionally, FNT is occasionally utilized to aid public health in the fight against infections like malaria (Eskandari *et al.,* 2012). Pesticides containing organophosphorus disrupt the function of acetylcholinesterase, which can lead to lasting nerve damage in people and ani (de Fátima Alves *et al.,* 2018). Organophosphates have been linked to major diseases such as genotoxicity (Taghavian *et al.,* 2016), diabetes (Shapiro *et al.,* 2016), neurotoxic effects (Liu *et al.,* 2015), gestational hypertension (Janssen *et al.,* 2015), teratogenesis (Seifert, 2016) and carcinogenesis (Zayed *et al.,* 2015). Fenitrothion, also known as O, O–Dimethyl O– (3–methyl–4–nitrophenyl) phosphorothioate, a toxic, water-insoluble secondary metabolite that degrades into fenitrooxon and 3–methyl–4–nitrophenol by hydrolysis and photodegradation (Khan *et al.,* 2017).

Impact of pesticides on terrestrial and aquatic life

Terrestrial life: Deforestation, diseases, foreign species, pesticides, a scarcity of local resources, and climate change have all been demonstrated to harm biodiversity (Jucker *et al.,* 2011; MacDougall *et al.,* 2013; Seibold *et al.,* 2019).

Acute and chronic toxicity's adverse effects are determined by various elements such as dose, chemical nature, exposure time, and route. Introduction to industrial toxins and other ecological pollutants in water and land-dwelling settings has been found to limit creatures' life spans in previous studies (Glassmeyer *et al.,* 2017; Richardson *et al.,* 2018; Ghaffar *et al.,* 2019; Ghaffar *et al.,* 2020). The most visible evidence of toxicity is the death of target and non-target exposed species, which reduces the number of species in the population, and the frequency of mortality rate is directly proportional to the potency and mechanisms of pesticide toxic effects. Furthermore, a decline in the number of members of one species in a community causes a reduction in the population size of other species with which the target species interact (Sánchez-Bayo, 2011).

FNT is distinguished by immediate and intensive absorption in the gastrointestinal system, as well as preferred accumulation in the liver and the blood (Afshar *et al.,* 2008).

According to previous research, FNT causes significant changes in several organs, including the brain, liver, kidneys, and reproductive organs (Afshar *et al.,* 2008; El-Demerdash, 2011; Taib *et al.,* 2014; Abdel-Ghany *et al.,* 2016). The liver is an essential organ in the body since it is responsible for detoxification, biotransformation and excretion of xenobiotics such as pesticides. The liver is vulnerable to harm after accumulating significant toxic substances because of its high blood supply and large concentration of enzymes involved in the metabolic transformation of foreign molecules and synthesis of metabolites (Jayusman *et al.,* 2014). FNT generates reactive metabolites such as fenitrooxon during the biotransformation process involving the enzyme cytochrome P450 (CYP) (Taib *et al.,* 2014). FNT has been related to liver enzyme disturbance, hepatocyte death, necrosis, leukocytic infiltration in the portal area and moderate blood vessel blocking in earlier studies (Afshar *et al.,* 2008; Elhalwagy *et al.,* 2008). FNT toxicity is linked with oxidative stress, which is caused due to excessive creation of reactive oxygen species (ROS), which causes harm to many cell compartments (El-Demerdash, 2011). FNT affects the endocannabinoid signaling pathway in male reproductive organs in experimental animals, inducing spermatotoxicity and testicular damage (Ito *et al.,* 2014; Taib, 2014).

***Aquatic life*:** Insecticides, herbicides, and fungicides are examples of pesticides, a class of potentially harmful compounds capable of affecting the structure and function of microbes in watery environments. Pesticides are used in around 2.6 billion pounds worldwide each year, with the United States accounting for 22% of global pesticide use. Agricultural pesticides account for over 80% of these chemicals, with only a small percentage utilized to manage structural and public health pests (Grube *et al.,* 2011).

Pesticides can be carried from application locations to surrounding rivers and streams by shallow groundwater

transport, precipitation, and irrigation runoff. Aquatic populations such as fish, cladocerans, benthic invertebrates, and other species can be harmed by pesticides in rivers and streams (Gilliom *et al.,* 2006; Belden *et al.,* 2007; Schäfer *et al.,* 2013; Moschet *et al.,* 2014; Nowell *et al.,* 2014; Smiley *et al.,* 2014; Nowell *et al.,* 2017). According to reports, environmental toxins are continuously and widely diffused in aquatic ecosystems, eventually building up in the tissues of exposed species from various sources (Sivashanmugam *et al.,* 2017; Amaroli *et al.,* 2018; Verma *et al.,* 2018; Baralić *et al.,* 2020). Freshwater habitats, in general, suffer from high biodiversity losses since they are the most vulnerable to many environmental contaminants (Gupta *et al.,* 2008; El-Murr *et al.,* 2015; Pisa *et al.,* 2015). Epidemiological studies are necessary to assess the acute and toxic consequences of a variety of environmental contaminants, including disinfection by-products, fluorinated chemicals, BPA, phthalates, pesticides, and synthetic endocrine disruptors (Smarr *et al.,* 2016; Barakat *et al.,* 2017; Rattan *et al.,* 2017; Adoamnei *et al.,* 2018; Karwacka *et al.,* 2019). In aquatic invertebrates, Fenitrothion has significant systemic toxicity, with LC50 values range from g/L for most species; fish, on the other hand, are less sensitive, with 96-LC50 values ranging from 1.7 to 10 mg/L for most species (ICPS, 1992). Neurotoxic endpoints are more sensitive than systemic toxicity endpoints as a neurotoxic agent, and fish exposed to low g/L doses of this substance have shown relevant behavioral impairments (Morgan *et al.,* 1990).

***Pesticide Toxicity and Risk (Hazard)*:** According to statistics, the death rate in developing countries has increased due to a lack of understanding about the toxicity of various agrochemicals, notably pesticides, and individuals are succumbing to significant illnesses, including cancer, kidney failure, and infertility (Zaluski *et al.,* 2015). Pesticides can enter the human body through the breath of pesticide-containing air, dust, or vapor; oral exposure through polluted food and water, as well as cutaneous exposure from pesticide contact (Sacramento, 2008). Pesticides are applied on foodstuff, like vegetables and fruits, and then leach in soils and groundwater, posing a threat to drinking water. Pesticide spray has the potential to harm the air. Chemical toxicity and the length and volume of exposure determine the degree of harm to human health (Lorenz, 2009). Chemical toxicity is determined by the type of toxicant, exposure routes (oral, cutaneous, and through breath), dosage and individual. Toxicity might be short-term or long-term. The ability of a chemical to cause harm in a short period after absorption, such as a few hours or a day, is referred to as acute toxicity. Chronic toxicity is the ability of a drug to cause unfavourable health effects when treated for an extended time. The toxicity of insecticides is commonly expressed as a 50 percent lethal dose (LD50) or a 50 percent lethal concentration (LC50). The LD50 is the single dose of poison needed to kill 50% of the test population in a genetically homogenous group. It is measured in milligrams per kilogram of body mass. The LC50 of a chemical is the concentration in the external media (typically the air or water around animal models) that causes 50% mortality in a genetically homogenous population. It is expressed in tenths of a millionth (ppm) (Yadav *et al.,* 2017).

Potential Impact on Human Health: Humans can be poisoned or injured through pesticides. Pesticides that harm inside the body's organs or systems produce poisoning, while pesticides that are external irritants cause injury. Some pesticides are highly hazardous to humans, and even little doses can have devastating consequences. Other active components are less poisonous, but they can nonetheless be harmful if consumed in excess. Pesticide exposure can cause moderate symptoms such as slight skin irritation or additional allergic indications, as well as more severe signs and symptoms such as severe dizziness, headache, or nausea. Specific pesticides, like organophosphates, might produce serious side effects like convulsions, unconsciousness and even death. Pesticide toxicity in humans can be defined by the type of contact, path, or body system affected. In general, poisons that are eaten are more poisonous than those inhaled, and poisons that are inhaled are more toxic than those absorbed via the skin (dermal exposure). While certain pesticides might cause reversible damage, complete recovery may take an extended period. Even if they are not lethal, other poisons may have irreversible effects (Damalas *et al.,* 2016).

***Synthesis of Organophosphorous*:** Organophosphorus compounds, as a family of organic chemicals, have gotten much attention from the synthetic community because of their wide range of applications in materials science (George *et al.,* 2008; Kirumakki *et al.,* 2009; Spampinato *et al.,* 2010), natural products (Tan *et al.,* 2014), medicinal chemistry (Dang *et al.,* 2011; Chen *et al.,* 2012), organic synthesis (Choudhury *et al.,* 2013) and ligand chemistry (Fernández *et al.,* 2011).

Several generic techniques for synthesizing organophosphorus compounds have been established during the last few decades, the most important of which is the C–P bond-forming strategy (Cohen *et al.,* 2003). Meanwhile, radical additions of phosphorus-centered radicals to unsaturated compounds have been identified as a powerful way for swiftly creating organophosphorus compounds and have gained much interest (Leca, 2005; Pan *et al.,* 2015; Luo *et al.,* 2017).

Detergents, agrochemicals and flame retardants all contain organophosphorus compounds (Emsley, 2000). In organometallic chemistry, coordination chemistry and metal-mediated organic synthesis, they can also be versatile ligands. White phosphorus (P4) accounts for the vast bulk of phosphorus atoms in organophosphorus compounds (Lynam, 2008). Because of their wide range of uses in the agrochemical, pharmacological, materials sciences, biological, synthetic organic and phosphorus-containing compounds have great synthesis potential (Demmer *et al.,*

2011). Phosphorus substituents control a wide range of biological, pharmacological, and material functions. Organic chemists operate as ligands or guidance groups in transition-metal catalysis and play key roles as crucial scaffolds in organic reactions (Moonen *et al.,* 2004; Mao *et al.,* 2017).

Fenitrothion: The flowable molecule Fenitrothion [O, O-dimethyl O-(4-nitro-m-tolyl) phosphorothioate] has the chemical formula C9H12NO5 PS. It is available in different emulsifiable quantities such as 95 percent and 50 percent (structural formula: Fig, 1). Organophosphate/contact insecticide is the chemical class, with definite gravity 1.3227; 1.32; 1.34; 1.3084 at 20 °C (Rani *et al.,* 2018).

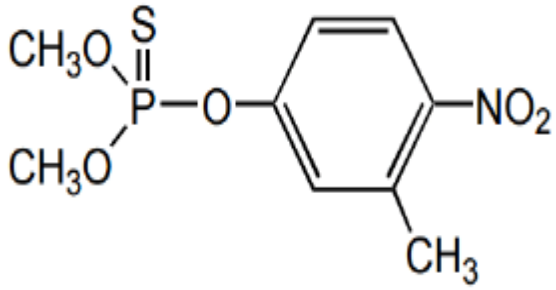

Figure 1. The structural formula of Fenitrothion

Fenitrothion (FNT) is an organophosphate pesticide that is widely used around the world. It was classed as a class II (moderately hazardous) compound by the World Health Organization (WHO) in 2010, and it was labeled as a "red list" item by the European Union (EU) due to its toxicity to aquatic life (Kozawa *et al*., 2009).

***Mechanism of action*:** Fenitrothion is a neurotoxin and acetylcholinesterase inhibitor that forms a strong covalent bond with the acetylcholinesterase enzyme, which catalyzes the creation of acetylcholine (Rani *et al.,* 2018). Though, as a by-product of FNT metabolism by cytochrome P450, large amounts of reactive oxygen species (ROS) are formed. FNT suppresses acetylcholinesterase activity, but it also has a dangerous side effect by releasing too many reactive oxygen species (ROS), which causes lipid peroxidation and oxidative damage to proteins, polyunsaturated fatty acids, and nucleic acids (Budin *et al.,* 2013; Budin *et al.,* 2014). Earlier research had revealed that OP, particularly FNT, affects the functioning of different tissues/organs in animals and humans, causing the emergence of a variety of clinical disorders (Budin *et al.,* 2013; Budin *et al.,* 2014; Taib *et al.,* 2015; Abdel-Ghany *et al.,* 2016; Saber *et al.,* 2016). FNT can cross through the placenta, causing foetal toxicity and post-implantation losses, as well as reducing fetal viability (Fahmi *et al.,* 2018). 3-methyl-4-nitrophenol, a FNT decay product isolated from DEPs, was discovered to have harmful effects on animal and human health (Li *et al.,* 2006). DEPs (Yun et al., 2009) and FNT (Galal et al., 2019) are (ROS) which can oxidize proteins, lipids, and DNA, as well as cause mitochondrial dysfunction and death (Ibrahim *et al.,* 2020). Theprimary mechanism against ROS formation is activating antioxidant enzymes such as superoxide dismutase (SOD), which protects the cell from the damaging effects of superoxide radicals by converting them to less harmful H_2O_2 and then elimination catalase (CAT). Furthermore, thiols are important in the non-enzymatic and enzymatic scavenging of reactive oxygen species (ROS), and thiol/disulfide equilibrium is required for detoxification, signaling, and inflammatory disorders (Dogru *et al.,* 2016).

Absorption: After oral administration, FNT is rapidly removed from the body, whereas its metabolites are rapidly absorbed through the gastrointestinal tract (Mueller, 2001). As a result, FNT is relatively safe for mammals (Budin *et al.,* 2013). FNT is distinguished with rapid and intensive absorption in the gastrointestinal systemand preferred accumulation in the liver and blood (Afshar *et al.,* 2008). Pesticides must first be absorbed by humans who have been exposed to them, most notably at the gastrointestinal level in the case of oral exposure; neurotoxic pesticides must also penetrate the blood-brain barrier before they can have toxicodynamic effects (Coecke *et al.,* 2013). Medication absorption in the intestine and distribution in the brain are also significant challenges, especially as the industry grows (Abbott, 2004; Jones *et al.,* 2016).

***Toxicological Effects*:** Fenitrothion is poisonous and inhibits algal development at chronic levels. Fenitrothion is hazardous to crayfish and other environmental creatures, and honeybees and rats are significantly poisoned by it. It causes cancer in humans. Fenitrothion residues are persistent in the environment and must be eliminated (Rani *et al.,* 2018).

***Animal and human toxicity*:** Due to their widespread use, organophosphorus pesticides unavoidably infiltrate surface and groundwater supplies, causing severe health and environmental risks (Bolat *et al.,* 2018). Insecticides containing organophosphorus can impair acetylcholinesterase function, resulting in irreversible brain damage in people and animals (de Fátima Alves *et al.,* 2018). Current investigations showed that organophosphates might cause severe diseases like genotoxicity (Taghavian *et al.,* 2016), diabetes (Shapiro *et al.,* 2016), teratogenesis (Seifert, 2016), gestational hypertension (Janssen *et al.,* 2015) and carcinogenesis (Zayed *et al.,* 2015). Fenitrothion (FNT) [O, O-dimethyl O-(4-nitro-m-tolyl) phosphorothioate], because it is efficient against mosquitoes, flies, and cockroaches prevalent in farms, this insecticide is often used to decrease insect damage to rice, cereals, cotton, and vegetables (Ensafi *et al.,* 2017; Larki, 2017). Furthermore, FNT is sometimes utilized to aid public health in the fight against infections like malaria (Eskandari *et al.,* 2012).

The main indications of OPs poisoning in the respiratory system are shortness of breath and fast progressive bradypnea

advancing to apnea due to losing central inspiratory drive, resulting in significant breathing failure (Carey *et al.,* 2013).

***Effects on the brain*:** Organophosphate, a neurotoxicant, might affect the most favourable prenatal growth, differentiation of multiple tissues, including the brain, changing cell production and resulting in brain dysfunction. Prenatal exposure to organophosphates produces biochemical and neurobehavioral issues even at low dose levels, demonstrating that the developing brain is very vulnerable to these pesticides (Ouardi *et al.,* 2019) because they can pass the placental and blood-brain barrier (Bradman *et al.,* 2003). Fenitrothion (FNT), an organophosphate pesticide, is widely used in agriculture to advance food quality by reducing vector-borne disease transmission (Villaverde et al., 2008). FNT is rapidly absorbed and extensively incorporated from the digestive tract of mammals, where it is principally transported to numerous organs, including the nervous system (Afshar *et al.,* 2008).

FNT has adverse effects on the brain via suppressing acetylcholinesterase (AChE) activity, including headaches, sweating, Parkinson's disease, memory problems, and mental or neuropsychological issues (Sarikaya *et al.,* 2004). Acetylcholine accumulates throughout the nervous system when AChE is inhibited, leading muscarinic and nicotinic receptors to become overstimulated. In exploratory rats, neuronal necrosis has been reported in multiple cortical and subcortical locations after exposure to FNT (Alam et al., 2019). Fenitrothion is a pesticide that acts directly on central nervous system of parasites and is regarded as extremely harmful to living beings due to its effects upon thyroid hormone levels, brain neurotransmitter levels and gonadal and sensory deprivation (McLachlan *et al.,* 2001).

***Genotoxic effect of Fenitrothion*:** The purpose of determining if substances have adverse effects on future generations of humans and providing mechanistic insights on carcinogenicity, whether the mode of action is genotoxic or non-genotoxic, is the goal of a teratogenic effect (Horibe *et al.,* 2018The generation of (ROS), that damage cell components, is assumed to be the origin of Fenitrothion's toxic effect (Goel *et al.,* 2005). Oxidative stress is known to disturb the oxidant-antioxidant equilibrium, resulting in alterations in cell function, cellular macromolecules, and eventually cell death (Kehrer, 1993). Furthermore, Fenitrothion inhibits acetylcholinesterase function, causing nervous system disruption and complete loss of nuclear intactness, conformational abnormalities in rat liver and kidney cells, including full nuclear membrane destruction, abnormally expanded smooth endoplasmic reticulum (Kumar *et al.,* 1993).

Epidemiological studies reveal that using organophosphorus insecticides like FN may cause increased DNA damage and lower concentrations in human sperm, which can be fatal to future generations (Suzuki *et al.,* 2013). During pregnancy, DEPs and/or FNT generated oxidative stress in foetal cardiac cells, which resulted in apoptosis, DNA damage, and various histopathological abnormalities, and these effects were replicated in the combination (Ibrahim *et al.,* 2020).

***Effect on production and immunity*:** Pesticides only reach the intended pests in roughly 0.1 percent of cases, with the remainder spreading through the soil, water, and food (Galloway *et al.,* 2003; Mahboob *et al.,* 2014). Acute OP poisoning is a global health issue that kills 100,000 people per year (Gunnell *et al.,* 2007).

The spleen, being the body's largest major immunological organ, is vital to maintaining immune homeostasis. The spleen (or splenic cells/splenocytes) is a vulnerable target for poisons and insecticides in both *in vivo* and *in vitro* experiments (Li *et al.,* 2011; Medjdoub *et al.,* 2011; Dhouib *et al.,* 2015; Kuang *et al.,* 2016; Wang *et al.,* 2017). FNT lowers the spleen/body and thymus/body weight ratios, inhibits the synthesis of T cell-derived cytokines interleukin (IL)-2 and interferon (IFN-) (Nakashima *et al*., 2002), and lowers splenic T-lymphocyte proliferation (Li *et al*., 2011). Excessive reactive oxygen species (ROS) and oxidative stress are connected to FNT toxicity (Elhalwagy *et al.,* 2008; Budin *et al*., 2012; Liu *et al*., 2018).

***Adverse effects of Fenitrothion on blood cells*:** Because fish blood components diminish because of any form of environmental change, and because they are directly linked through the gill surface, they respond fast to any variation in water quality, blood indicators have been pushed as biomarkers in toxicity research (Islam *et al.,* 2019).

Toxic metals and pesticides in water can damage fish by altering normal behavior (Satyavardhan *et al.,* 2013; Rani *et al.,* 2014), physiological function (changes in blood parameters) (Mohammod *et al.,* 2015; Balmuri *et al*., 2017; Renieri *et al.,* 2017), histo-morphological alterations in the intestine, kidney, liver, etc., depletion of DNA, RNA and protein contents (Sadiqul *et al.,* 2016). Fish red blood cells (erythrocytes) differ from mammalian red blood cells in that they have cell nuclei, and these differences are viewed as significant biomarkers of pollution in the form of morphological changes. The genotoxicity and mutagenic impacts of numerous environmental contaminants have been assessed using red blood cell micronucleus assays (Bolognesi *et al.,* 2011; Sadiqul *et al.,* 2016; Islam *et al.,* 2019). FNT treatment reduced hepatocyte viability in a time and dose-dependent way, according to a previous study (El-Shenawy *et al.,* 2010) and produced reproductive damage in rats (Struve *et al.,* 2007). The *in vitro* FNT reduced the production of interferon (IFN)-g and interleukin (IL)-2 and impeded the development of human peripheral blood mononuclear cells (Nakashima *et al.,* 2002). FNT treatments resulted in a significant drop in splenic and thymic indices, improved thymic atrophy, and immune system modulation in mice and

rats, according to the other *in vivo* study (Moon *et al.,* 1986). Shortly, FNT is immunotoxic.

***Effects on liver and kidney*:** Fenitrothion is a direct-acting insecticide commonly used on cereals, rice, cotton, and vegetables to control insect pests and mites (El-Demerdash, 2011). FNT is defined by quick and intensive gastrointestinal absorption, as well as preferential accumulation in the blood and liver (Afshar *et al.,* 2008). According to an earlier study, FNT produces extreme variations in multiple organs, including the brain, kidneys, liver, and reproductive organs (Afshar *et al.,* 2008; El-Demerdash, 2011; Taib *et al.,* 2014; Abdel-Ghany *et al.,* 2016).

The liver is essential to the body since it is the principal organ for detoxification, biotransformation, and excretion of xenobiotics, including pesticides. The liver is vulnerable to harm after amassing significant levels of hazardous substances because of its huge blood supply and higher concentrations of enzymes involved in the metabolic transformation of foreign molecules and synthesis of metabolites (Jayusman *et al.,* 2014). FNT generates reactive metabolites, including fenitrooxon, during the biotransformation process involving the enzyme cytochrome P450 (CYP) (Taib *et al.,* 2014). In previous studies, FNT exposure was connected to liver enzyme disruption, hepatocyte death, necrosis, portal leukocytic infiltration, and moderate blood vessel congestion (Afshar *et al.,* 2008; Elhalwagy *et al.,* 2008). FNT toxicity has been linked to oxidative stress, which is caused by the increased creation of reactive oxygen species (ROS), which causes harm to many cell compartments (El-Demerdash, 2011). Due to metabolite synthesis, the liver, as the principal organ for drug metabolism and detoxification, is constantly exposed to xenobiotic-induced harm (Jaeschke *et al.,* 2002). The liver's function can be affected since it is the first organ to contact with ingested nutrients, drugs, and chemicals, particularly OP pesticides (Al-Attar, 2010). At a dose of 20 mg/kg body weight, FNT was found to induce harm to the liver and kidneys (Elhalwagy *et al*., 2008), pancreas (Budin et al., 2012), and sperm and testes (Taib *et al*., 2013) of experimental rats. Long-term exposure to organophosphorus insecticides causes kidney failure (Attia *et al*., 2009). According to research, pesticide exposure has also been linked to kidney cancer (Kalender *et al.,* 2010). Variations in hepatic biomarkers like serum aminotransferase and direct and indirect bilirubin show that they induce metabolic, ultrastructural, mitochondrial and biochemical harm in the liver (Avsarogullari *et al.,* 2006; Hoekstra *et al.,* 2013).

***Effects on reproductive system*:** OP is metabolized in the liver by CYP450, and when mitochondrial respiration is disrupted due to OP exposure, reactive oxygen species (ROS) production rises (Lukaszewicz-Hussain, 2010). ROS-generating systems like mitochondria, xanthine-oxidases, NADPH-oxidases, and CYP450s, as well as a large amount of polyunsaturated fatty acids (PUFA) in the testis, render the testis vulnerable to ROS (Aitken *et al.,* 2008). Increased reactive oxygen species (ROS) in the testis disturbs homeostatic antioxidant defense systems, resulting in increased oxidative harm to lipids, proteins, and DNA (Aitken *et al.,* 2008). Apoptosis in germ cells may be accelerated as a result of this disruption. Apoptosis is a biological process that occurs in the mammalian testis and controls spermatogenic cell development. On the other hand, pesticides and other xenobiotics can cause a rise in the number of apoptotic germ cells in rats (Gawish *et al.,* 2010). The stress response can be expressed by cells responding to stressful events, as demonstrated by the rise in heat shock protein (HSP) expression (Feng *et al.,* 2001). HSPs are a type of stress protein found in testis, and their involvement in male reproduction is becoming more and more well-known. HSP70 (70 kDa HSP) is a molecular chaperone that aids in the folding, assembly, and disassembly of protein complexes (Feng *et al*., 2001). The etiology of male infertility has been connected to aberrant HSP70 expression. As a result, reproductive toxicology research on this stress protein is critical (Feng *et al.,* 2001). The expression of HSP70 in testis constantly increases after interacting with xenobiotics such as OP and organochlorine, indicating oxidative stress (Saradha *et al.,* 2008). Furthermore, oxidative stress has been demonstrated to affect male reproduction by disrupting a diversity of physiological systems in the male reproductive tract, including spermatogenesis, resulting in biochemical and morphological alterations (Agarwal *et al.,* 2004). Various biochemical parameters in rats exposed to OPs have been observed to change, including total cholesterol, protein, and sialic acid, associated with male reproductive failure (Joshi *et al.,* 2003; Joshi *et al.,* 2007; Joshi *et al.,* 2012). An imbalance between the formation of reactive oxygen species (ROS) and the mechanisms of enzymatic and non-enzymatic antioxidants as a bodily protective system causes oxidative stress. The main mechanism of injury after chronic exposure to organophosphates has been identified as oxidative stress (Lukaszewicz *et al.,* 2010). Furthermore, excessive levels of polyunsaturated fatty acids (PUFA) in the plasma membrane of sperm cells may result in oxidative stress-related alterations (Agarwal *et al.,* 2006). Chronic exposure to the insecticide Fenitrothion resulted in histopathological alterations in P. clarkii's hepatopancreas, testis, and ovary. The degree of alteration in these tissues is determined by the length of the exposure and the animal's capacity to overcome Fenitrothion poisoning (Abdel Mageed, 2004). Pesticides include 2,4-D, chlorpyrifos, glyphosate, diazinon, endosulfan, Fenitrothion, lindane, dieldrin, DDT, DDE, mancozeb, permethrin, and thiram are endocrine disruptors (ED) (McKinlay *et al.,* 2008; Thongprakaisang *et al.,* 2013). Endocrine disruption is a toxicity mechanism that disrupts the hormonal communication between cells, tissues, and organs,

resulting in reproductive abnormalities, decreased fertility and fecundity, sex ratio changes, spontaneous abortion, precocious puberty, polycystic ovary syndrome, impaired immune function, and neurobehavioral disorders, as well as a variety of malignancies (McKinlay *et al.,* 2008). PNP (4-nitrophenol) and PNMC (3-methyl-4-nitrophenol) may cause reproductive failure in males and females by causing oxidative stress in the cell. Lipid peroxidation, as well as a decrease in glutathione peroxidase and superoxide dismutase activity, occur when chicken spermatogonial cells are exposed to PNMC (Mi *et al.,* 2010). By decreasing the expression of oestrogen receptors, PNP and PNMC limit ovarian steroidogenesis (Zhang *et al*., 2017). Even though they contain antioestrogenic (Li *et al*., 2008), oestrogenic (Taneda *et al*., 2004; Furuta *et al*., 2005; Li *et al*., 2006), or anti-androgenic (Taneda *et al*., 2004; Furuta *et al*., 2005; Li *et al*., 2006) activities; nevertheless, the role and mechanism of their action in the female reproductive system. PNMC has been found to produce endocrine disruption in immature (Li *et al*., 2007) and adult (Li *et al*., 2008) female Japanese quail (*Coturnix japonica*) by affecting the hypothalamopituitary-gonadal axis and related reproductive processes at the central level. According to Li *et al*. (2008), PNMC lowers luteinising hormone (LH) and oestradiol (E2) levels in the blood plasma of egg-laying Japanese quail while enhancing progesterone levels. In previous *in vitro* studies, PNP and PNMC were reported to significantly inhibit steroid hormone release from chicken ovarian follicles (Sechman *et al.,* 2020). PNMC is also referred to as a FNT degradation product (Bhushan *et al.,* 2000).

***Conclusion*:** Food is a more fundamental human necessity than shelter or clothing, and it fulfills the body's nutritional needs for growth, maintenance, repair, and reproduction. Crop protection measures have a big impact on agricultural productivity. The primary goal of pesticide use is to improve food security, with an improved standard of living as a secondary goal. The presence of toxic levels in the environment leads to cellular level harmful changes as well as many grossly observed alterations in metabolism, productivity, reproduction potential and general health status of the exposed animals/humans. This review uncovered numerous negative effects of FNT on the cellular level, hematological, hepatic and renal systems, male and female reproductive organs, and neurological systems. Keeping in the notice the adverse effects of improper use of pesticides government should make policies for the proper pesticide use and educating farmers about pesticides' adverse effects on health.

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